Mixed Xylenol Category - Comments of Environmental Defense

(Submitted via Internet 12/17/02)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for xylenol isomers.

The test plan for xylenol isomers was prepared by Merisol USA LLC. This plan is very similar to a companion plan on ethylphenol isomers submitted by Merisol on the same date. There are 6 isomers included in this plan, namely 2,3-xylenol, 2,4-xylenol, 2,5-xylenol, 2,6-xylenol, 3,4-xylenol and 3,5-xylenol. They are used as intermediates in the manufacture of a wide variety of products such as resins, flame retardants, antioxidants and insulating varnishes.

Surprisingly, there are no data available on the xylenols deemed reliable for use by the HPV Challenge Program. Accordingly, the sponsor proposes a complete spectrum of studies to provide data on chemistry, environmental fate, health effects and ecotoxicity. The proposed studies would be conducted on a mixture containing equal amounts of all 6 isomers. The sponsor contends that all of the isomers should possess the same toxicological and environmental fate properties based on available data for the corresponding methylphenol isomers (cresols) including a very thorough set of studies conducted by the NTP. In these studies, the cresols demonstrated a low order of toxicity but some genetic toxicity assays (i.e. cell transformation) were positive. The cresols, like the xylenols, contain a free hydroxyl group that renders these molecules readily biodegradable.

We agree with the sponsor's proposal to conduct a full spectrum of HPV studies on a mixture of xylenol isomers. However, we recommend that cytotoxicity studies be used instead of acute toxicity tests in rodents. Inasmuch as these substances likely possess low acute toxicity and high-dose data will be obtained from the range-finding component of the repeat dose study, conducting separate acute toxicity tests in rodents is an unnecessary use of animals.

Although the sponsor's contention that the xylenols and cresols possess similar toxicological and environmental properties is probably true, we do have some concerns that once the data come in this contention could be contradicted by indications that the xylenols should not be handled as a category (i.e., if the initial round of data indicate that the category is not "well behaved"). While such an outcome would be somewhat surprising, the current near-total absence of data on these xylenols means that it cannot be ruled out. Thus, after data are generated under this test plan, they should be reviewed to determine if in fact the category performs as anticipated; if it does not, generation of additional data for the HPV endpoints for the individual members of the category will be needed (members of the public should be given the opportunity to comment on this).

In the meantime, we recommend that the sponsor conduct molecular studies to help verify that the six isomers belong in the same category. In particular, we recommend that the sponsor conduct gene-expression studies in in vitro systems using microarray technologies to determine if all the isomers produce the same pattern of gene-expression changes. These data are not required by the HPV program but they would, in conjunction with the studies already proposed by the sponsor, provide a solid database to indicate whether or not the xylenols category is scientifically justified.

Thank you for this opportunity to comment.

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